Amendments to the Claims

Claims 1-19 (cancelled)

Claim 20 (currently amended): A type I polyketide synthase according to claim 43 ~~17~~, wherein the ~~loading module's loading functionality is provided by an acyltransferase-type~~ acyltransferase domain ~~having~~ has an arginine residue in the active site.

Claim 21 (cancelled)

Claim 22 (cancelled)

Claim 23 (previously added): A type I polyketide synthase according to claim 20, wherein said acyltransferase domain is specific for loading with malonyl.

Claim 24 (previously added): A type I polyketide synthase according to claim 20, wherein said acyltransferase domain is specific for loading with methylmalonyl.

Claim 25 (previously added): A type I polyketide synthase according to claim 20, wherein said acyltransferase domain is specific for loading with ethylmalonyl.

Claims 26-28 (cancelled)

Claim 29 (currently amended): A type I polyketide synthase according to claim 43 ~~17~~, wherein ~~at least the KSq domain of said loading module corresponds to the KSq domain of~~ the loading module is selected from the loading module of the polyketide synthase multienzyme of oleandomycin, spiramycin, niddamycin, methymycin, tylosin or monensin ~~wherein KSq represents the N-terminal ketosynthase-like domain of a~~

~~loading module in which there is a glutamine residue in place of the active site cysteine residue of a KS domain of an extension module which is essential for beta-ketoacyl-ACP synthase activity~~.

Claim 30 (currently amended): A type I polyketide synthase according to claim 43 ~~17~~, wherein said polyketide synthase is adapted to synthesize a polyketide selected from

(a) 12- ~~and 16-~~membered macrolides with acetate starter units;

(b) 12~~, 14~~ and 14 ~~16~~-membered macrolides with propionate starter units;

(c) variants of rifamycin, avermectin, rapamycin, immunomycin and FK506 which differ from the natural compound in the incorporation of ~~with~~ acetate starter units or propionate starter units; or

(d) a polyketide wherein the starter unit gave rise to a sidechain selected from allyl and hydroxymethyl.

Claims 31-42 (cancelled)

Claim 43 (currently amended): A type I polyketide synthase which produces a 12- or 14- membered macrolide and which comprises a loading module and a plurality of extension modules, wherein said loading module is adapted to load an optionally substituted malonyl and then to effect decarboxylation of the loaded residue to provide a corresponding optionally substituted acetyl residue for transfer to the first of said extension modules, wherein at least the first of said extension molecules is not naturally associated with a loading module that effects decarboxylation of an optionally substituted malonyl, and wherein said loading module is of the form:

(natural-KSq) ~~(Dec)~~ -(AT)-(ACP)

wherein ACP represents an acyl carrier protein domain, AT represents an acyltransferase domain which is adapted to load an optionally substituted malonyl; and natural-KSq ~~Dec~~ represents a domain which effects ~~is adapted to effect~~ decarboxylation of ~~a~~ the loaded optionally substituted malonyl; said natural-KSq domain corresponding to a natural ketosynthase (KS) domain which differs from a KS domain of an extension module by having a glutamine residue in place of a cysteine in the active site; wherein the polyketide produced by the polyketide synthase is other than a 14-membered macrolide having a 13-methyl group due to incorporation of an unsubstituted acetate starter ~~wherein at least one of the domains is heterologous to other domains of the loading module or is an engineered domain~~.

Claim 44 (new): A type I polyketide synthase according to claim 43, wherein the polyketide produced is a 12-membered macrolide.

Claim 45 (new): A type I polyketide synthase according to claim 43, wherein the polyketide produced is a 14-membered macrolide.

Claim 46 (new): A type I polyketide synthase which produces a polyketide and which comprises a loading module and a plurality of extension modules, wherein said loading module is adapted to load an optionally substituted malonyl and then to effect decarboxylation of the loaded residue to provide a corresponding optionally substituted acetyl residue for transfer to the first of said extension modules, wherein at least the first of said extension molecules is not naturally associated with a loading module that effects decarboxylation of an optionally substituted malonyl, and wherein said loading module is of the form:

(natural-KSq)-(AT)-(ACP)

wherein ACP represents an acyl carrier protein domain, AT represents an acyltransferase domain which is adapted to load an optionally substituted malonyl; and natural-KSq represents a domain which effects decarboxylation of the loaded optionally substituted malonyl; said natural-KSq domain corresponding to a natural ketosynthase (KS) domain which differs from a KS domain of an extension module by having a glutamine residue in place of a cysteine in the active site; wherein the acyltransferase domain is derived from any extension module of a type I polyketide synthase; wherein the polyketide produced by the polyketide synthase is other than a 14-membered macrolide having a 13-methyl group due to incorporation of an unsubstituted acetate starter.

Claim 47 (new): A type I polyketide synthase according to claim 46, wherein said acyltransferase domain is specific for loading with malonyl.

Claim 48 (new): A type I polyketide synthase according to claim 46, wherein said acyltransferase domain is specific for loading with methylmalonyl.

Claim 49 (new): A type I polyketide synthase according to claim 46, wherein said acyltransferase domain is specific for loading with ethylmalonyl.

Claim 50 (new): A type I polyketide synthase according to claim 46, wherein said acyltransferase domain corresponds to the acyltransferase of module 6 of the niddamycin polyketide synthase.

Claim 51 (new): A type I polyketide synthase according to claim 46, wherein said acyltransferase domain corresponds to

the acyltransferase of module 4 of the FK506 polyketide synthase.

Claim 52 (new): A type I polyketide synthase according to claim 46, wherein the natural-KSq domain of the loading module is selected from the KSq domain of the loading module of the polyketide synthase multienzyme of oleandomycin, spiramycin, niddamycin, methymycin, tylosin or monensin.

Claim 53 (new): A type I polyketide synthase according to claim 46, wherein said polyketide synthase is adapted to synthesize a polyketide selected from

(a) 12- and 16-membered macrolides with acetate starter units;

(b) 12, 14 and 16 membered macrolides with propionate starter units;

(c) variants of rifamycin, avermectin, rapamycin, immunomycin and FK506 which differ from the natural compound in the incorporation of acetate starter units or propionate starter units; or

(d) a polyketide wherein the starter unit gave rise to a sidechain selected from allyl and hydroxymethyl.

Claim 54 (new): A type I polyketide synthase which produces a polyketide and which comprises a loading module and a plurality of extension modules, wherein said loading module is adapted to load an optionally substituted malonyl and then to effect decarboxylation of the loaded residue to provide a corresponding optionally substituted acetyl residue for transfer to the first of said extension modules, wherein at least the first of said extension molecules is not naturally associated with a loading module that effects decarboxylation of an optionally substituted malonyl, and wherein said loading module is of the form:

(engineered-KSq)-(AT)-(ACP)

wherein ACP represents an acyl carrier protein domain, AT represents an acyltransferase domain which is adapted to load an optionally substituted malonyl; and engineered-KSq represents a domain which has been genetically engineered to effect decarboxylation of a loaded optionally substituted malonyl by mutating the active site cysteine residue to a glutamine residue; wherein the polyketide produced by the polyketide synthase is other than a 14-membered macrolide having a 13-methyl group due to incorporation of an unsubstituted acetate starter.

Claim 55 (new): A type I polyketide synthase according to claim 54, wherein the acyltransferase domain has an arginine residue in the active site.

Claim 56 (new): A type I polyketide synthase according to claim 55, wherein the acyltransferase domain is a natural extension module acyltransferase domain.

Claim 57 (new): A type I polyketide synthase according to claim 54, wherein the engineered-KSq and acyltransferase domain pair produced by mutation occur together in an extension module in their unaltered state.

Claim 58 (new): A type I polyketide synthase according to claim 55, wherein said acyltransferase domain is specific for loading with malonyl.

Claim 59 (new): A type I polyketide synthase according to claim 55, wherein said acyltransferase domain is specific for loading with methylmalonyl.

Claim 60 (new): A type I polyketide synthase according to

claim 55, wherein said acyltransferase domain is specific for loading with ethylmalonyl.

Claim 61 (new): A type I polyketide synthase according to claim 56, wherein said acyltransferase domain corresponds to the acyltransferase of module 6 of the niddamycin polyketide synthase.

Claim 62 (new): A type I polyketide synthase according to claim 56, wherein said acyltransferase domain corresponds to the acyltransferase of module 4 of the FK506 polyketide synthase.

Claim 63 (new): A type I polyketide synthase according to claim 54, wherein said polyketide synthase is adapted to synthesize a polyketide selected from

(a) 12- and 16-membered macrolides with acetate starter units;

(b) 12, 14, and 16-membered macrolides with propionate starter units;

(c) variants of rifamycin, avermectin, rapamycin, immunomycin and FK506 which differ from the natural compound in the incorporation of acetate starter units or propionate starter units; or

(d) a polyketide wherein the starter unit gave rise to a sidechain selected from allyl and hydroxymethyl.